Rheumination

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Disclosures

- None
  - “I’m just a simple country doc hiding in a university”
Goals

• To expose the audience to new and relevant medical information in the field of Rheumatology.
• To discuss how this information impacts patients with rheumatic diseases.
• To examine how this information impacts providers and the numerous specialists that participate in the care of these complex patients.
There are many disease states that can impact the lung of a patient with RA.

- RA nodules
- Pneumonitis
- Infections
- Cancer
- Bronchiolitis
- Obliterans bronchiolitis
- ILD

Risk factors for ILD
- Male sex, tobacco use, RF(+), CCP(+)

Interstitial Lung Disease
Rheumatoid Arthritis

Interstitial Lung Disease

- There may also be a genetic risk factor that is seen with IPF (Juge et al., NEJM, 2018).
  - The gain-of-function MUC5B promoter variant rs35705950
- On CT scan the pattern may be more of a UIP pattern and this pattern may actually herald the onset of RA
  - This would be in distinction to MTX induced hypersensitivity pneumonitis which is typically early in therapy and is subacute (Kiely, et al., BMJ, 2019).

Rheumatoid Arthritis

RA Drugs

• Large topic but a few pearls for the newest drugs/biological therapy
• For most of these drugs the patient should be screened for hepatitis B, C, and TB
  • Hep B-s ag
  • Hep B-s ab
  • Heb B-core IgM
  • Hep C ab
  • TB tine or TB quantiferon
• Avoid concomitant use with other biologicals
• Avoid the administration of live vaccines
• Increased risk of certain malignancies to include lymphoma
Rheumatoid Arthritis

RA Drugs

- Abatacept
  - Selective T cell co-stimulation modulator
  - COPD patients may develop more respiratory adverse events
- Anti-TNF therapies (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab)
  - Infections to include fungal
  - Demyelination
  - Lupus-like syndromes
  - Heart failure

Rheumatoid Arthritis

RA Drugs

• Tofacitinib
  • JAK inhibitor that is a oral small molecule
  • Increased risk of GI perforations
  • Decreased white cells, increased lipid and increased liver enzymes
  • Questionable/probable risk of thrombosis

• Baricitinib
  • JAK inhibitor
  • Increased risk of thrombosis

• Tocilizumab
  • IL-6 RA
  • GI perforations
  • Decreased white cells, increased lipid and increased liver enzymes
• The Rheumatologist, 2019. [https://www.the-rheumatologist.org/article/rheumatology-drugs-at-a-glance-part-3-rheumatoid-arthritis/10/](https://www.the-rheumatologist.org/article/rheumatology-drugs-at-a-glance-part-3-rheumatoid-arthritis/10/)
Rheumatoid Arthritis

Myocarditis

• It has been suggested that RA has an increased risk of myocarditis (Amigues et al., Arthritis Rheumatol., 2019)
• With the use of PET scanning increased uptake was noted in 49/119 patients (39%)
• Uptake seemed to parallel RA disease activity
• Question
  • What impact does this finding have on heart disease and heart failure?

Rheumatoid Arthritis

Gut bacteria and RA

• “Hey Doc, antibiotics make my arthritis better”
• We know that there exists a link between periodontitis and RA likely through two pathogens
  • *Aggregatibacter actinomycetemcomitans*
  • *Porphyromonas gingivalis*
• There may be other bacteria pathogens as well with *Prevotella capri*
  • Impacts the balance with *Bacteriodes*
• These research findings may eventually lead to the link of mucosal injury and autoimmunity and impact treatment choices
Rheumatoid Arthritis

Check Point Inhibitors

- Check point inhibitors are used widely in oncology care. Two commonly targeted checkpoints include:
  - CTLA-4
  - PD-1
    - Blockage enhances T cell function and tumor lysis
- These drugs are associated with immune-related adverse events from self tolerance
- Myalgia/arthralgia, GI, skins, hepatic, and endocrine system abnormalities have all been described
- May require immunosuppressants to treat
Systemic Lupus

Toll Like Receptors (TLR)

• Toll-like receptors are important immune surveillance.
• TLR-7 has been implicated in the pathogenesis of lupus and more recently so has TLR-9 (Celhar, et al., Arthritis Rheumatol. 2018).
• In the case of TLR-9, disease is the result of ablation.
  • The result of research in TLR-9 deficient mice
• This study supports the importance of bench research colleagues in the development of new novel therapies
Systemic Lupus

Depression

- We all know that depression is often seen in patients with chronic illness
- This study suggested that depression may be a risk factor for the development of lupus (Roberts, et al., JAMA Psychiatry, 2018)
  - Study used two large cohorts of patients assessed over 20 years
  - Diagnosis used the ACR criteria
- It may be reasonable to spend time asking question about autoimmunity symptoms in your patients with depression.
Systemic Lupus
Cardiovascular risks

• Patient with lupus have a higher incidence of CV risk factors despite their female sex and lower age prevalence
• Research has demonstrated that these patients have less screening and treatment for these risk factors (Chen, et al., Arthritis Care & Research, 2019)
  • These patients also have less statin prescriptions
Systemic Lupus

ANA Testing

• ANA testing is a constant source of aggravation
• Researchers took sera from patients with lupus and analyzed their sera on three commercially available kits (Pisetsky, et al., Ann Rheum Dis., 2018)
  • Poor overall correlation especially with the ELISA kits
  • Suggested one of the two approaches
    • ELISA or multiplex for screening followed by an ANA by IFA
    • Start with the ANA by IFA and then a multiplex to assess for other antibody positivity.

Gout

Prevalence

- Chen-Xu, et al. reported that the prevalence of gout was 3.9% in US adults (9.2 million people between 2015-2016)
  - 5.2% in men
  - 2.7% in women
- Hyperuricemia rates were approximately 20% in the same population
  - Rates increase with age
- These rates have remained stable since 2007
- Treatment rate for gout was approximately 33%
- Chen-Xu, et al., Arthritis Rheumatol. 2019
Gout

Allopurinol and renal disease

• Study looked at the risk of CKD and progression in allopurinol users (Vargas-Santos, et al., JAMA Intern Med., 2018)
• Looked at stage 1 and stage 2 CKD
  • Allopurinol 300 mg initiated in newly diagnosed gout
    • Those in the allopurinol group had a 13% lower risk of progressing to stage 3 CKD at a mean follow up of 5 years
    • Smaller allopurinol doses did not have the same impact
• When facing worsening CKD in a gout patient on allopurinol look for other causes
  • https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2705694
  • https://www.therheumatologist.org/article/allopurinol-for-gout-an-unlikely-contributor-to-kidney-disease/?singlepage=1
Gout

Febuxostat and cardiovascular risks

- The FDA recently placed a CV warning on febuxostat
- This was the result of a study by White, et al. in the NEJM (2018)
  - 6190 patients received either allopurinol or febuxostat from 32-85 months
  - 56.6% discontinued the trial regimen and 45% discontinued follow up
  - The primary endpoint was a composite of:
    - Cardiovascular death
    - Nonfatal MI
    - Nonfatal stroke
    - Unstable angina with urgent revascularization
Gout

Febuxostat and cardiovascular risks

- The primary endpoint composite score was:
  - 10.8% in the febuxostat arm
  - 10.4% in the allopurinol arm
- A pre-specified analysis of all-cause mortality and CV mortality demonstrated:
  - A hazard ratio for CV death of 1.34 (CI 1.03-1.73) in the febuxostat arm
- Discuss CV issues with patients and preferentially use allopurinol
  - https://www.the-rheumatologist.org/article/study-finds-newer-gout-drug-poses-risk-heart-patients/?singlepage=1
Erosive OA

Treatment options

Deformity
Node
Bony enlargement
Osteophyte
JSN
Hyperextension of the first metacarpo-phalangeal joint
JSN and subchondral sclerosis
Slight squaring of the thumb base

https://www.nature.com/articles/s41584-018-0095-4?WT.feed_name=subjects_osteoarthritis
Erosive OA

Treatment options

• Symptomatically these patients have inflammatory complaints
• European League Against Rheumatism (EULAR) guidelines suggest:
  • Focus is on symptomatic therapy and not anti-inflammatory therapy
  • Avoid systemic therapy. Instead try:
    • Topical NSAIDs
    • Splints
  • There is a role for limited joint injections
  • There is a role for Chondroitin sulfate

https://www.the-rheumatologist.org/article/what-to-do-with-erosive-inflammatory-osteoarthritis/?singlepage=1
Erosive OA

Treatment options

• I personally have used DMARDs though the data is slim to none.
  • Hydroxychloroquine
  • Minocycline
  • methotrexate

• Recent study looked at the use of etanercept for erosive OA with swollen joints and found no symptomatic improvement after 24 weeks
  • Kloppenburg, et al., Ann Rheum Dis., 2018
  • https://ard.bmj.com/content/early/2018/10/03/annrheumdis-2018-213202
Knee OA

Novel therapy

- To date, like other forms of OA, treatments remain symptomatic
- Injection therapy includes both steroids and hyaluronic derivatives
- Some are pushing “stem cell therapy”
- Editorial to follow:
  - We are not talking about multipotent stromal cells from the bone marrow or umbilical cord blood and we are not talking about embryonic stem cells
  - Expensive
  - Not covered by insurance
  - Not proven
Knee OA

Novel therapy

• Yazici, et al., Osteoarthritis Cartilage, 2017, looked at the utility of an injectable small molecule which a Wnt pathway inhibitor
  • Demonstrated symptomatic improvement for up to 12 months
    • https://www.ncbi.nlm.nih.gov/pubmed/28711582

• Other are looking at gene therapy, which has been explored and found to be effective in large and small animals
  • Nixon, et al., Arthritis Rheumatol., 2018
    • https://onlinelibrary.wiley.com/doi/10.1002/art.40668
ACR guidelines
Reproductive issues and medications

• The ACR guidelines are in review currently though excerpts were presented at the 2018 National meeting.
• Men trying to conceive:
  • Discontinue cyclophosphamide 12 weeks before and thalidomide four weeks before attempting to conceive
  • Continue hydroxychloroquine, colchicine, azathioprine, TNF inhibitors, sulfasalazine, methotrexate, leflunomide, mycophenolate, cyclosporine, tacrolimus, anakinra and rituximab
  • Consider semen analysis if a man has trouble conceiving while on sulfasalazine
    • SAZ can be associated with reversible fertility issues
ACR guidelines
Reproductive issues and medications

• Women trying to conceive or become pregnant:
  • Medications to stop during pregnancy:
    • cyclophosphamide, thalidomide, mycophenolate, methotrexate and leflunomide,
    • ANY previous leflunomide should prompt a “wash out” before pregnancy and immediately if pregnant
  • Avoid NSAIDs in the third trimester
  • Medications that may be continued during pregnancy:
    • hydroxychloroquine, sulfasalazine, and azathioprine
    • Continue TNF-inhibitors during pregnancy if clinically necessary
      – Be aware of data of using live vaccines with caution, for one year, in babies born to mothers who used anti-TNF therapy during pregnancy
  • Low dose non-fluorinated steroid therapy if needed
• I often use high risk OB for pregnancy planning
Cannabis Terminology

• **Cannabis**—The scientific and historical name for the tall, bushy, fast-growing, cane-like weed used as a drug by humans for thousands of years. The female unfertilized flower buds are the most potent.

• **Cannabinoids**—The active ingredients in marijuana, like THC and CBD; there are about 60-100 cannabinoids.

• **CBD**—Cannabidiol— the second most common active ingredient in cannabis. Does not cause euphoria and may be a powerful anti-inflammatory, antispasmodic and antianxiety drug.

• **THC**—Tetrahydrocannabinol— the main active ingredient in marijuana. Isolated in 1967. It causes euphoria. Most research on medical efficacy for pain, nausea and spasms comes from studies with THC.
  • Hemp which is less than 0.3% THC/20%+ CBD
  • Marijuana which is more than 20% THC/10%+CBD
Cannabis

Terminology

• Terpenes are common, often aromatic, organic compounds found in many plants.
  • Cannabis plants have over 120 identified terpenes with different aromas.
  • There may be an association with psychoactive effects for strains and smells.
  • They reduce the intoxicating effects of THC when consumed together and add additional therapeutic value.
Two types of hemp oil –
  • one is pressed from the hemp stalks
  • one is from the seeds
• Hempseed oil (oil pressed from the seeds) has been used for years and is used as a moisturizer in many beauty products - Hempseed oil is listed as a cannabis sativa seed oil
• CBD only oil comes from Hemp extract. (<0.3% THC) also called Hemp Oil
• Cannabis oil would contain CBD, THC and terpenes
• This matters because the CBD oil is more expensive and has a variety of legal ramifications
Cannabis

Concentrate types

• Tinctures
• Topicals
• Capsules
• Vaporizers
• Many types of edibles.
• The cannabis of the 60’s and 70’s had maybe at most 4% THC
• Some products now tested have ranges of 20% to 45% THC with little CBD content
• CBD products are not federally regulated
  • May not be any CBD in CBD oils
  • Possibility of multiple contaminants
Cannabis
Prevalence

- Rheumatic disease registry (FORWARD) patients asked if they had ever used marijuana, cannabis or cannabidiol (CBD)
- Among 11,006 respondents the prevalence of past or current cannabis use has increased from 6.3% in 2014 to 17.6% in 2019
- At both time points, patients reporting use were younger, had worse measures on all PROs and were likely to have a history of smoking cigarettes, have fibromyalgia, report a history of depression and report opioid use
Cannabis
Legality issues in Nebraska

- 1 of 3 States where marijuana is illegal
- **Fact 1** - If a police officer catches you buying, possessing or smoking pot, it is a ticket or a jail sentence
- **Fact 2** - If you buy hemp seed oil in a store there will be **no legal action**
- **Fact 3** - There is much confusion of what to do with CBD or cannabidiol oil
- State Attorney General states that CBD is illegal
- Douglas County Attorney states that his law enforcement officers will not target businesses selling CBD products
- The Nebraska Farming Act - LB657 - allows industrial hemp to be grown in Nebraska
  - 10 groups have received the go ahead
  - There were 176 requests
- Problem - How to tell how much CBD or THC is in the hemp plants without labs in Nebraska testing

Slides: Courtesy of Michelene Heath-Holmes, MD
Rheuminations
Closing thoughts and Questions